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EXPERT OPINION

Gene Therapy in Erectile Dysfunction: Dead or Alive?

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Erectile dysfunction (ED) is a common disorder—about 50% of males between the ages of 40 and 70 are affected.[1] Currently, there is (at least via public perception) a notion that ED treatments for mild to moderate ED have been very successful. Treatment for most men is based on pharmacotherapy with phosphodiesterase (PDE) type 5 inhibitors;[2] however, besides pharmacotherapy, the treatment of ED has been managed by numerous approaches, including, for example, vacuum constriction, intracorporal injection therapy, intraurethral alprostadil, penile implants, revascularization, platelet-rich plasma, and stem cell therapy.[3,4] Although many patients with ED experience high efficacy with PDE type 5 inhibitors, this therapy is inadequate in approximately 30−40% of patients, and particularly in some specific groups such as diabetic men.[5] In addition, PDE inhibitors can result in adverse effects; moreover, some patients may not be eligible for this therapy, for example, patients receiving nitrates who are at a risk of developing hypotension. Thus, there is still a significant unmet medical need for the development of more effective therapeutic strategies for the treatment of ED.

In this regard, gene therapy has recently attracted increased attention as a treatment for a variety of different diseases/conditions—as reflected in the steady and increasing number of gene therapy-related applications (ie, publications) to the eye, liver, and cancer, for example (Figure 1). Compared to these therapeutic areas, the number of publications on gene therapy for ED treatment has been extremely modest—with the first publication in 1997,[6] and with no obvious increase in publication activity during the last decade. In fact, despite the rather dramatic advances in gene transfer vectors, development of new vector delivery methods, and discovery of new gene targets, translational progress for the treatment of ED has been slow, and few approaches have been applied clinically. Importantly for the field, in 2017, the U.S. Food and Drug Administration approved the first gene therapies to be marketed in the United States for the treatment of lymphoblastic leukemia, large B-cell lymphoma, and retinal dystrophy,[7] and more recently (2019; https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/approved-cellular-and-gene-therapy-products), approval has also been given for the treatment of, for example, prostate cancer, spinal muscle atrophy, and melanoma.

Nonetheless, in the end, the application of gene therapy for ED represents an exciting opportunity to push the field forward—as suggested by the recent spate of published reviews.[3,4,8−10] In fact, gene therapy for ED may provide the best therapeutic option for patients with, for example, severe cardiovascular disease, nitrate prescriptions, diabetes, obesity, and those who have undergone radical prostatectomy. Moreover, gene therapy for ED has 4 major intrinsic advantages: (i) the penis is easily accessible and the desired gene can be administered directly into the corporal tissue, without entering the systemic circulation; (ii) corporal vascular smooth muscle cells of the penis have a relatively low turnover rate, thus allowing a desired gene to be expressed for long periods of time; (iii) the vascular smooth muscle cells of the penis are interconnected by gap junctions permitting relatively low transfection efficiency due to the resulting syncytial smooth muscle cell network; and (iv) transduced genes to the penis may affect any aspect of the erectile process by selectively altering the expression of a given molecular target, and thus, target disease-specific gene products that may improve the erectile response.[11]

Although several preclinical studies for ED treatment have provided promising results, gene therapy has not yet reached utility in clinical practice. As ED is not a life-threatening condition, the application of gene therapy requires a high safety level. Clinical studies using naked DNA gene therapy with a plasmid (*hSlo*) expressing the human large conductance, voltage dependent, Ca^{2+} sensitive K channel (hMaxi-K channel) represent the only gene therapy to be evaluated in phase 1 clinical trials to date.[12−14] The promising primary safety outcomes of the study, coupled to preliminary indications of effectiveness, suggest that hMaxi-K gene transfer may offer advantages both from safety and delivery aspects and possibly, efficacy aspects.

CONCLUSION

There is still very scarce public/general recognition of the unmet medical need for improved ED treatment of the growing clinical population. However, gene therapy for ED is not dead but remains a hopeful and novel therapeutic area for the treatment of ED. This may be particularly applicable to patients who respond poorly to the PDE5 inhibitors.

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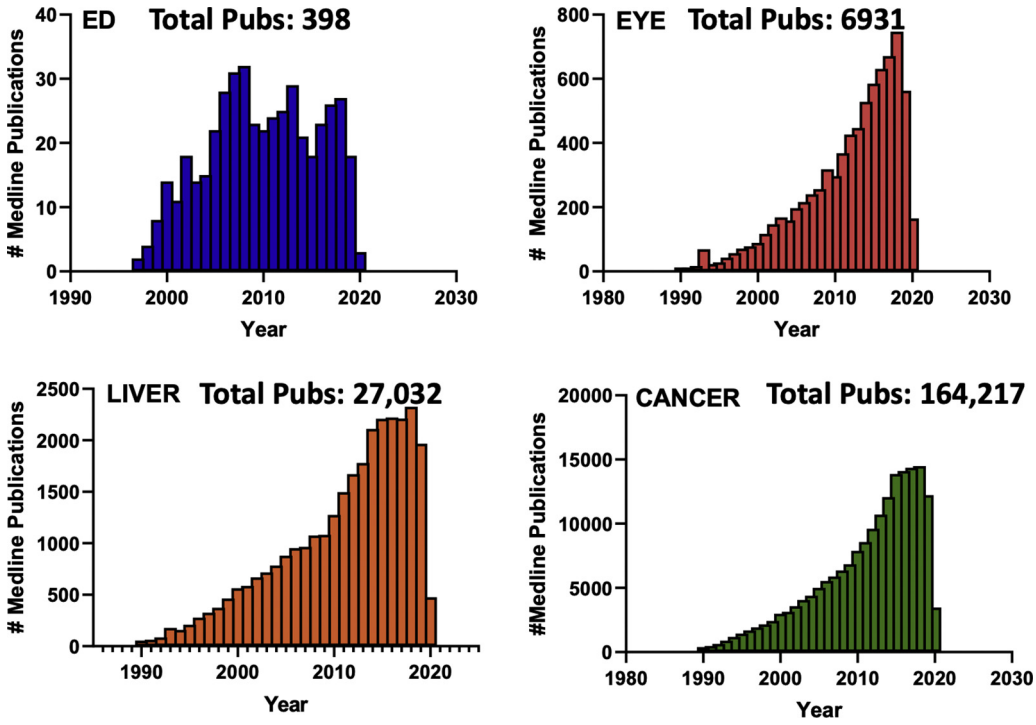

Figure 1. Number of gene therapy-related articles publications in erectile dysfunction (ED) compared to treatments of other medical conditions such as the eye, liver, and cancer. Articles were identified by using the Medical Subject Headings of "gene therapy" and crossing it with the organ/tissue/condition of interest. Figure 1 is available in color online at www.jsm.jsexmed.org.

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